MATHEMATICAL MODELING OF THE CHEMICAL REACTION NETWORK THAT PROTECTS MITOCHONDRIA IN HUMAN NEURAL CELLS FOLLOWING TRAUMATIC BRAIN INJURY

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"Following traumatic brain injury, human neural cells experience an increase in reactivity between peroxynitrite and superoxide dismutase. This reaction prevents superoxide dismutase from performing its essential role in the cell, which is to act as a catalyst in a reaction which protects mitochondria in the cell from damage (Bayir, 2007). Since mitochondria are vital to a cell's survival, it is desirable to understand the mechanism that a cell uses to protect itself from harm when these reactions occur. The goal of this research is the mathematical development of these processes using the techniques of chemical kinetics, so that we may gain understanding of the complicated system of chemical reactions governing this mechanism. This mathematical development includes analyzing the concentration versus time of all reactants, discovering the time scales when they react, and analyzing which reactions in particular influence the tendency of the concentration of a particular reactant to reach equilibrium. This analysis and the interpretation of the results will provide mathematical support for the proposed protection mechanism, furthering our understanding of how the brain cell behaves under the stress of traumatic head injuries. We find that this system can indeed be modeled by a system of ordinary differential equations, whose solution can be interpreted to accurately describe the system. The oxidation percentages and ratios of the different enzymes involved can be plotted and interpreted, and the amount that each reaction forces the concentration of each reagent to change at turning points can be determined."

I. MATHEMATICAL MODELING OF MITOCHONDRIAL PROTECTION

A major topic in the field of chemical kinetics is studying the rate at which reactions occur and how the concentrations of reactants in a chemical reaction change with time. A basic result from this field states that the rate at which a reaction occurs is directly proportional to the concentration of the reactants (de Mol, 2010). This law, known as the rate law, makes it possible to model, given a system of chemical reactions, the rate of change of each reactant's concentration with ordinary differential equations. This concept can be applied to very complex systems of reactions relatively easily.

Techniques from the field of chemical kinetics can be applied directly to computational biology, where the systems of chemical reactions studied occur inside human cells. Most human cells, including the brain cells studied in this paper, contain mitochondria. Mitochondria are organelles responsible for, among other things, producing adenosine triphosphate, which the cell uses as a source of chemical energy. Therefore, the healthy function of the cell is entirely dependent on the mitochondria being healthy (Mcbride et al., 2006). Damage to mitochondria is responsible for cardiac dysfunction (Lesnefsky, 2001) and other mitochondrial disorders (Gardner, 2005). Even the aging process and eventual death of cellular organisms is related to the function of mitochondria (Terman, 2010). Since the mitochondria play such a vital role to the cell, it would be beneficial to the cell to minimize any chemical having a detrimental effect on the mitochondria. Therefore, it is of vital importance to the advancement of cellular biology and healthcare applications that reactions damaging or inhibiting the function of mitochondria be understood, and in particular, what the cell does to defend against such reactions.

A medical application based on the study of how mitochondria defend themselves is related to brain cells (Bayir, 2007). Essentially, the following reactions tend to protect the mitochondria from damage in neural cells following traumatic brain injury. Superoxide ($O_2^{\bullet-}$) is produced in mitochondria. The enzyme superoxide dismutase (SOD) prevents nitric oxide from reacting with the superoxide, a reaction that would form peroxynitrite, which is harmful to enzymes. So, there must be a sufficient amount of SOD present to prevent these harmful reactions from occurring and thus to prevent damage to the mitochondria. These processes are described in greater detail by Rafikov et al. (2007). The goal of this paper is the mathematical development of these processes using the techniques of chemical kinetics.

In the given chemical network, pictured in Figure 1 (K. Hosking, pers. comm., August 11, 2009), a mechanism is proposed to "protect" the enzyme catalysts nitric oxide synthase (NOS), SOD, and catalase (CAT). An enzyme is protected when it reacts with hydrogen peroxide (H_2O_2). This is called oxidation and is denoted by a plus sign following the symbol for the enzyme catalyst. An enzyme is "infected" when it reacts with peroxynitrite ($ONOO^-$), and it cannot perform its function (Bayir, 2007). This is called nitration and is denoted by a minus sign following the symbol for the enzyme catalyst. When an enzyme reacts with hydrogen peroxide, it can perform its normal function while being "blocked" from reacting with peroxynitrite. An enzyme is said to be free if it has not been oxidized or nitrated and a free enzyme is denoted by placing a zero after its symbol. If a certain proportion of the free enzymes are nitrated by peroxynitrite before they perform their function, or before they are oxidized by hydrogen peroxide, the cell can no longer sustain its mitochondrial function and dies. Within the brain cell, there is an initial concentration of CAT0, SOD0, and NOS0 of approximately 10-3 moles per liter, as well as a large concentration of molecular hydrogen (large compared with the concentrations of the other reagents). As mentioned above, mitochondria produce superoxide under such stresses as traumatic injury. At time zero, a disturbance of the cell causes the mitochondria to inject superoxide at a constant rate, k1, into the cell, and an external reaction to the system shown in Figure 1, catalyzed by NOS0, injects nitric oxide ($NO^{\bullet}$) into the region near mitochondria. At early times, the superoxide can react in three ways: 1) with nitric oxide to produce peroxynitrite, 2) with molecular hydrogen to produce hydrogen peroxide, and 3) with molecular hydrogen catalyzed by SOD to produce hydrogen peroxide. Once all of the ingredients are present, the following reactions occur: 4) hydrogen peroxide reacts with CAT0, SOD0,

and NOS0, 5) peroxynitrite reacts with CAT0, SOD0, and NOS0, 6) an external reaction is catalyzed by the NOS+ and injects nitric oxide into the environment, 7) hydrogen peroxide decays into water, 8) hydrogen peroxide leaves the environment and 9) nitric oxide leaves the environment. All of the results assume that reactions 7 through 9 happen at slow enough rates to be neglected. This assumption has a negligible effect on the concentrations on the timescale considered in this study.

At very long times (approximately 60 seconds), the following trends are predicted based on Rafikov's physical intuition about the system: the superoxide, hydrogen peroxide, and the nitric oxide concentrations will reach a stable terminal value, while the peroxynitrite will increase linearly (pers. comm. June, 2009). The

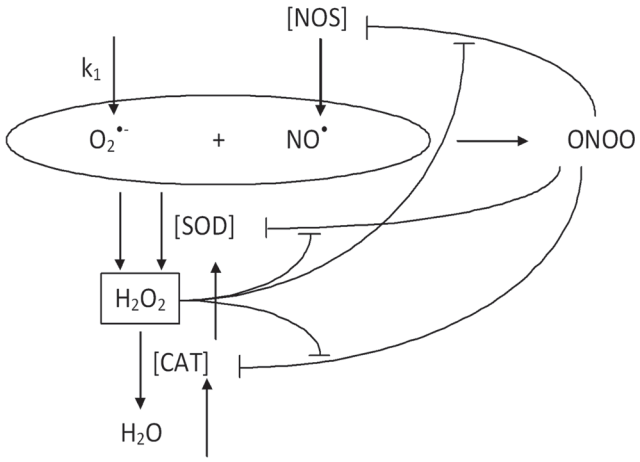

Figure 1. The chemical network describing the mechanism by which mitochondria defend themselves inside human neural cells following traumatic brain injury. Enzymes are contained in brackets, the lines with bars at one end show the enzyme nitration and oxidation reactions, and the arrows show all other reactions.

free enzymes will decay to zero on the same timescale (about 60 seconds) as they either get oxidized or nitrated, and the oxidized and nitrated enzymes will reach a terminal value as the free enzyme runs out.

The purpose of this study is to, for the first time, mathematically quantify the system of reactions describing the process by which mitochondria in human brain cells defend themselves following traumatic brain injury. This mathematical quantification includes calculating the concentration in time of all reactants involved, determining which reactions influence the tendency of the concentrations to stabilize, discovering the timescale during which these processes occur, and calculating the oxidation ratio and percent as a function of the physical parameters of the system of reactions. All of these results are obtained, but more knowledge, which is currently unknown, such as the exact initial concentrations of the reagents and the rate at which they react with each other, is required for an exact mathematical description.

II. METHOD

The system of equations given in Table 1 was solved using Matlab R2008a. The function ode23tb was employed, a solver recommended by Mathworks for solving stiff systems of differential equations (Mathworks, 2009). Stiffness can be interpreted as resulting from the difference in scale of the reaction rates. For the calculations of various derivatives below, the symbolic manipulation shell in Matlab R2008a was used.

The variable associations are given in Table 2.

The following vector is used for the reaction constants (k_i is the i^{th} entry):

$k=(10^{-3},10^{5},7\times10^{9}, 8\times10^{6},10^{3.15},0,10^{10},2\times10^{-1},0,10^{3},10^{3},10^{3})$.

The equations in Table 1 give the rate of change of the concentration of each reactant. The estimated value for each k_i gives the rate at which the two reactants it multiplies react, or in some cases, the probability that the one ingredient it multiplies will react. The k_i are determined by Rafikov in part by previous experimental data (pers. comm.). The units of concentration in these equations are moles per liter. The unit of time is seconds. Since the overall units must balance, the reaction rate constants have varying units, depending on whether the term they are in is linear or quadratic in concentration. The construction of the

equations can be understood by comparing the terms on the right hand sides to Figure 1. For example, the right hand side of the equation giving the rate of change of superoxide concentration, equation (1a), has four terms. The first term gives the rate at which superoxide is initially injected into the system. The second term denotes the decrease in superoxide due to its reacting with molecular hydrogen in the environment and producing hydrogen peroxide. The third term denotes the same reaction, but catalyzed by the free and oxidized SOD. The last term denotes the decrease in superoxide due to its reacting with nitric oxide and producing peroxynitrite. All of the equations can be constructed in this way. Note that some of the reaction constants have been set to zero. These constants are associated with reactions (8) and (9), hydrogen peroxide and nitric oxide leaving the environment, which are assumed to be negligible on the timescales analyzed in this study.

Reaction modeling equations	
$\dot{x}_1 = k_1 - k_2 x_1 - k_3 x_1 (x_8 + x_{10}) - k_9 x_1 x_3$	(1a)
$\dot{x}_2 = k_2 x_1 + k_3 x_1 (x_8 + x_{10}) - k_4 x_2 (x_{11} + x_{13})$ $-k_5 x_2 x_5 - k_6 x_2 x_8 - k_7 x_2 x_{11} - k_8 x_2$	(1b)
$\dot{x}_3 = k_{10}(x_5 + x_7) - k_9 x_1 x_3 - k_{11} x_3$	(1c)
$\dot{x}_4 = k_9 x_1 x_3 - k_{12} x_4 x_5 - k_{13} x_4 x_8 - k_{14} x_4 x_{11}$	(1d)
$\dot{x}_5 = -k_5 x_2 x_5 - k_{12} x_4 x_5$	(1e)
$\dot{x}_6 = k_{12} x_4 x_5$	(1f)
$\dot{x}_7 = k_5 x_2 x_5$	(1g)
$\dot{x}_8 = -k_6 x_2 x_8 - k_{13} x_4 x_8$	(1h)
$\dot{x}_9 = k_{13} x_4 x_8$	(1i)
$\dot{x}_{10} = k_6 x_2 x_8$	(1j)
$\dot{x}_{11} = -k_7 x_2 x_{11} - k_{14} x_4 x_{11}$	(1k)
$\dot{x}_{12} = k_{14} x_4 x_{11}$	(1l)
$\dot{x}_{13} = k_7 x_2 x_{11}$	(1m)

Table 1. The differential equations modeling the system of reactions in Figure 1.

Most of the solutions to this system of equations have the general feature where they increase or decrease at a nearly constant rate and then reach equilibrium. It is useful to know which reaction in the network is most responsible for driving the concentration towards equilibrium. This happens twice in the most well behaved set of solutions (a set of solutions is considered well behaved if it is continuous, non-oscillatory, and finite), at two different time

Reactant	*Variable*
$O_2^{\bullet -}$	x_1
H_2O_2	x_2
$NO^{\bullet}$	x_3
$ONOO$	x_4
NOS^0	x_5
NOS^-	x_6
NOS^+	x_7
SOD^0	x_8
SOD^-	x_9
SOD^+	x_{10}
CAT^0	x_{11}
CAT^-	x_{12}
CAT^+	x_{13}

Table 2. The variable associations that are made between the chemical reactants and the variables of the differential equations

scales. The dependence of the turning points on the different reactions at the first temporal stabilization point is calculated. This first stabilization happens almost immediately.

It is a result of elementary differential calculus that when a graph reaches a local maximum or minimum, the first derivative equals zero, and the second derivative measures the magnitude and tendency for the graph to curve up or down. It is useful to proceed by making a few approximations which are valid at very

short times, solving for the stabilization values of a few of the reactants, and constructing formulae for the second derivatives of each reactant. Then the dependence of each of these equations on the various reactions can be measured by taking the partial derivative of each equation with respect to each reaction rate k. Now, plots can be constructed showing the dependence of the second derivative concentration formulae on each reaction rate. This is done by taking the magnitude of the partial derivative of each second derivative formula with respect to each reaction rate k_i, and plotting this versus the subscripts of the k_i. These plots have the subscript of each reaction constant along the x axis simply for visual clarity.

The graphs of the concentrations of superoxide, nitric oxide, and hydrogen peroxide increase very rapidly when the reaction starts. At this timescale, almost all of the enzymes are free. So, take

$\dot{x}_1=\dot{x}_2=\dot{x}_3=0$. When the graphs level off, $x_6=x_7=x_9=x_{10}=x_{12}=x_{13}=0$.

When these simplifications are made, the first temporal equilibrium concentration values of superoxide and hydrogen peroxide can be solved for, shown in Table 3.

Now, the second derivative of the concentration of each reactant in terms of these stabilization values can be calculated, taking the same approximations into account (Table 4). Where

$$X = x_{1,stable}(k_2+k_3x_8) - x_{2,stable}(k_4x_{11}+k_5x_5+k_6x_6+k_7x_{11}). \qquad (4)$$

The partial derivatives of equation (3a) with respect to each reaction constant are shown in Table 5 as an example.

III. RESULTS

The graphical solutions to the system of equations modeling the concentrations of the reactants are shown in Table 6. The unit of concentration in all of the graphs is moles per liter and the unit of time is seconds. The graphs for x_8 and x_{11} are identical to the graph for x_5, the graphs for x_9 and x_{12} are identical to the graph for x_6, and the graphs for x_{10} and x_{13} are identical to the graph for x_7. These solutions are interpreted in the discussion section.

The example of a graphical representation of the magnitudes of the partial derivatives of the second derivative concentration formula of superoxide shown in Figure 3 has been rescaled by dividing each magnitude by the corresponding k value, effectively putting each value on the same order of magnitude so the graph may be read easily. The positive points in this graph reflect the tendency for the associated reaction rate to cause positive curvature in the concentration graph at the first stabilization point, and the negative points give the concentration graph negative curvature. The magnitude of the point gives the relative influence of each reaction rate on the curvature of the concentration graph.

The quantity called oxidation ratio is defined to be the ratio of the terminal values of the oxidized enzyme to the nitrated enzyme. To measure how variations in k_1 and k_{10} affect the oxidation ratios of the different enzymes, a program was written which solves equations (1a)-(1m) for a matrix of k_1 and k_{10} values, where each ranges between two input values, records the oxidation ratio for each enzyme each time the system is solved, triangulates over the range of k_1 and k_{10} values and plots a surface showing the value of the oxidation ratio versus variation in k_1 and k_{10} (Figure 4).

Various other graphs can be produced to determine how variations in certain parameters will influence the percent of the initial amount of a certain enzyme that will be oxidized. These graphs could be useful if, for example, one needed to determine a value for k_1 or k_{10} for a desired oxidation percent without interpolating in three dimensions, shown in Figure 5. Another useful graph shows the first temporal stabilization value of superoxide, nitric oxide, or hydrogen peroxide (Figure 6) versus the oxidation percentage.

Stable concentration formulae

$$x_{1,stable} = \frac{k_1}{k_2 + k_3x_8} \qquad (2a)$$

$$x_{2,stable} = \frac{x_{1,stable}(k_2 + k_3x_8)}{k_4x_{11} + k_5x_5 + k_6x_8 + k_7x_{11}}$$

$$= \frac{k_1}{k_4x_{11} + k_5x_5 + k_6x_8 + k_7x_{11}} \qquad (2b)$$

Table 3. The stable values of superoxide and hydrogen peroxide at the first temporal stabilization point.

These could be used to predict the stabilization values of either of these reactants given the desired oxidation percentage.

IV. DISCUSSION

Despite being the first attempt to model this system of reactions mathematically, all of the goals stated in the introduction are accomplished. Namely, the concentration in time of all the reactants have been computed (Figures 2a-g). Reactions that

Second derivative formulae	
$\ddot{x}_1 = -k_9 k_{10} x_5 x_{1,stable}$	(3a)
$\ddot{x}_2 = x_{2,stable}^2 (x_5 k_5^2 + x_8 k_6^2 + x_{11} k_7^2)$	(3b)
$\ddot{x}_3 = k_{10} x_5 (-k_9 x_{1,stable} - k_{11})$	(3c)
$\ddot{x}_4 = k_9 k_{10} x_5 x_{1,stable}$	(3d)
$\ddot{x}_5 = x_5 (k_5 x_{2,stable})^2 - k_5 x_5 X$	(3e)
$\ddot{x}_7 = -k_5 x_{2,stable}^2 x_5 + k_5 x_5 X$	(3f)
$\ddot{x}_8 = x_8 (k_6 x_{2,stable})^2 - k_6 x_8 X$	(3g)
$\ddot{x}_{10} = -k_6 x_{2,stable}^2 x_8 + k_6 x_8 X$	(3h)
$\ddot{x}_{11} = x_{11} (k_7 x_{2,stable})^2 - k_7 x_{11} X$	(3i)
$\ddot{x}_{13} = -k_7 x_{2,stable}^2 x_{11} + k_7 x_{11} X$	(3j)
$\ddot{x}_6 = \ddot{x}_9 = \ddot{x}_{12} = 0$	(3k)

Table 4. The second derivative formulae for the concentrations of the reactants in terms of the first temporal stabilization values and the reaction rates.

influence the tendency of the concentrations to reach equilibrium can be determined through the second derivative dependence graphs (Figure 3), the timescale during which the reactions occur can be read off the plots in Figures 2a-g, and the oxidation ratio and percent can be calculated easily (Figures 4-5).

Partial derivative of second derivative formulae for $O_2^{\cdot-}$	
$\frac{\partial}{\partial k_1}\ddot{x}_1 = -\frac{k_9 k_{10} x_5}{k_2 + k_3 x_8}$	(5a)
$\frac{\partial}{\partial k_2}\ddot{x}_1 = -\frac{k_9 k_{10} k_1 x_5}{(k_2 + k_3 x_8)^2}$	(5b)
$\frac{\partial}{\partial k_3}\ddot{x}_1 = -\frac{k_9 k_{10} k_1 x_5 x_8}{(k_2 + k_3 x_8)^2}$	(5c)
$\frac{\partial}{\partial k_9}\ddot{x}_1 = -\frac{k_{10} k_1 x_5}{k_2 + k_3 x_8}$	(5d)
$\frac{\partial}{\partial k_{10}}\ddot{x}_1 = -\frac{k_9 k_1 x_5}{k_2 + k_3 x_8}$	(5e)
$\frac{\partial}{\partial k_4}\ddot{x}_1 = \frac{\partial}{\partial k_5}\ddot{x}_1 = \frac{\partial}{\partial k_6}\ddot{x}_1 = \frac{\partial}{\partial k_7}\ddot{x}_1 = \frac{\partial}{\partial k_8}\ddot{x}_1 = \frac{\partial}{\partial k_{11}}\ddot{x}_1 = \frac{\partial}{\partial k_{12}}\ddot{x}_1 = \frac{\partial}{\partial k_{13}}\ddot{x}_1 = \frac{\partial}{\partial k_{14}}\ddot{x}_1 = 0$	(5f)

Table 5. The partial derivatives with respect to the reaction rates of the second derivative of the superoxide concentration formula.

In what follows, when referring to a region inside the stressed human brain cell where mitochondria are present, the terms "the system" or "the environment of the system" will be used.

Superoxide, hydrogen peroxide, and nitric oxide all have two different temporal equilibrium points. The first temporal point of interest is reached very quickly, on the order of milliseconds, and the second point is reached after about 60 seconds (Figures 2a-g). Initially, the superoxide that has been injected into the system by the mitochondria builds up very rapidly and reacts on the same timescale with the large amount of molecular hydrogen in the environment to produce a lot of hydrogen peroxide very quickly. As this is happening, the nitric oxide is building up from the external reaction. When the first stability point is reached, the superoxide is split between reacting with the molecular hydrogen and the nitric oxide. Until the next and final stable point is reached, the superoxide continues to increase slightly as more is injected, the hydrogen peroxide continues to increase resulting from the increase in superoxide, and the nitric oxide decreases because the rate at which it reacts with superoxide to form peroxynitrite dominates the rate at which it is injected into the environment.

There is a slight delay in the production of peroxynitrite because all of the initial superoxide goes into producing hydrogen peroxide;

Graphical solutions to equations (1a)-(1m)

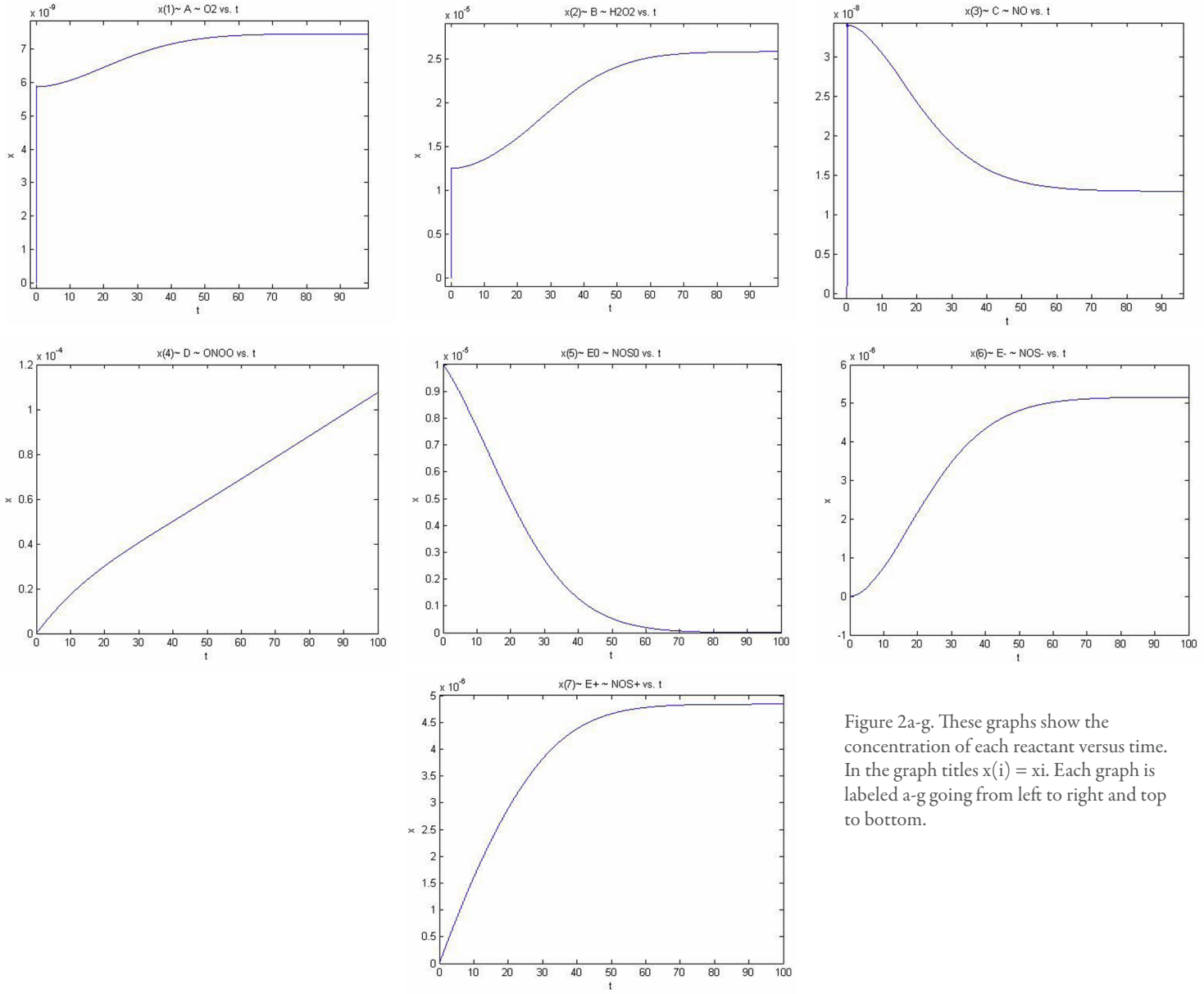

Figure 2a-g. These graphs show the concentration of each reactant versus time. In the graph titles x(i) = xi. Each graph is labeled a-g going from left to right and top to bottom.

it takes a short time for the reactants superoxide and nitric oxide to be devoted to producing peroxynitrite. After this, peroxynitrite increases linearly. If it is assumed that all the superoxide and nitric oxide goes into producing peroxynitrite and approximately none of the peroxynitrite goes into infecting the enzymes, the equation giving the rate of change of peroxynitrite reduces to an equation in which the growth is linear, namely $\dot{x}_4=k_9x_{1,stable}x_{3,stable}$, where superoxide and nitric oxide have reached their constant, stable values.

CAT0, whose initial concentration is 10-5 moles per liter, decays to zero in about 60 seconds. It splits into oxidized and nitrated CAT based on whether it bonds with hydrogen peroxide or peroxynitrite. After the same time-period, the CAT- and CAT+ level off to a terminal value because the entire amount of CAT0 has reacted. For this choice of parameters, the terminal values of CAT- and CAT+ are the same order of magnitude, showing that half the enzyme is protected, so the protection mechanism is highly pronounced. At the very beginning times, there is a slight delay in the production of CAT-, whereas the CAT+ increases rapidly. This is because there is a slight delay in the production of peroxynitrite whereas hydrogen peroxide gets produced very rapidly at the start. The analysis of SOD and NOS is similar to the analysis of CAT.

It is very difficult to give a direct interpretation of the second derivative dependence graphs (e.g. Figure 3) because the dependence is so complex. However, some general comments about the usefulness of these graphs can be made. These graphs show directly which reactions are responsible for causing the concentration to stabilize. In an experiment, one has certain control over the reaction rates, especially over the rate at which superoxide and nitric oxide are injected into the environment. Therefore, one of these graphs could be used to decrease the negative curvature at one of the turning points in a concentration graph by observing how varying reaction rates in a controlled experiment effects the magnitude of the negative points. This could be useful if one wished to delay the stabilization of NOS, allowing more time for the free NOS to prevent the formation of peroxynitrite, which, as was discussed before, is harmful to the mitochondria.

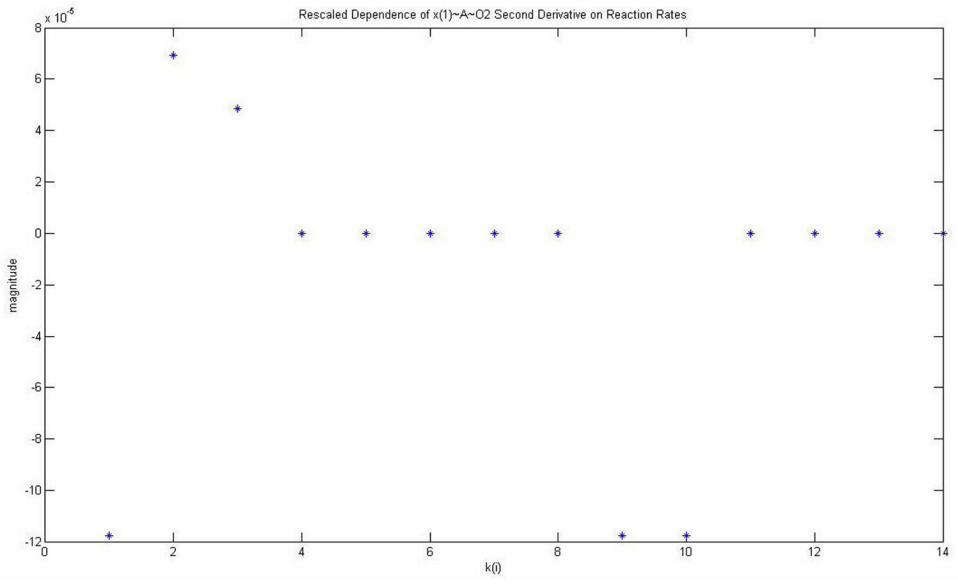

Figure 3. Dependence of x1 second derivative on reaction rates.

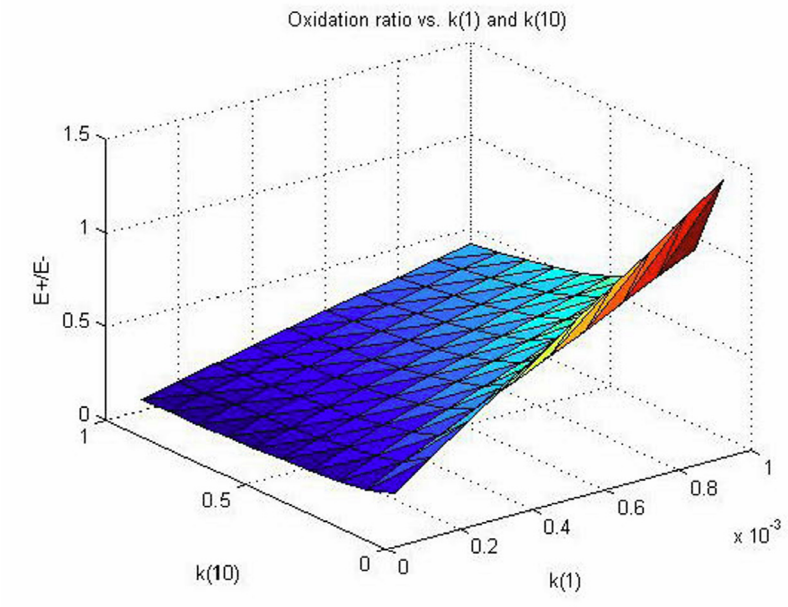

Figure 4. Oxidation ratio versus variation in k1 and k10.

The same analysis for the second temporal stabilization points is not so straightforward. It is very difficult to solve for the stabilization values of superoxide or hydrogen peroxide explicitly as before because of the dependence on x3 ,x4, and the oxidized and nitrated enzymes. So, the formulas for the second derivatives would depend on more than just the constants and initial enzyme values. The approximations which led to the formulae for the first temporal stabilization point forced the second derivatives of some of the reactants to equal zero. If similar substitutions are made for the second temporal stabilization point, nearly all of the second derivative formulae equal zero, and any further analysis would be trivial. One way around this would be to take the values of x3 and x4 at the turning points into account when evaluating the derivatives, but this would skew the dependencies. Unfortunately, this is the most biologically relevant information; showing that an enzyme's stabilization is highly dependent on the reaction between the enzyme and superoxide would show that the protection mechanism detailed in the introduction is highly pronounced in the system. Another method to analyze the dependence of the turning points on each reaction should be developed.

Fortunately, there is another way to analyze how pronounced the proposed protection mechanism is in the system: the oxidation ratio (Figure 4). The oxidation ratio measures directly how prominent the protection mechanism is; a ratio of approximately one means that an equal amount of enzyme is being oxidized as nitrated, meaning that about half the enzyme concentration can still perform its proper function. An experimenter has a certain amount of control over the reaction rates, particularly k1 and k10, the rates at which superoxide and nitric oxide are injected into the environment. These graphs could be useful to, for example, extrapolate the required k1 and k10 for a desired oxidation ratio.

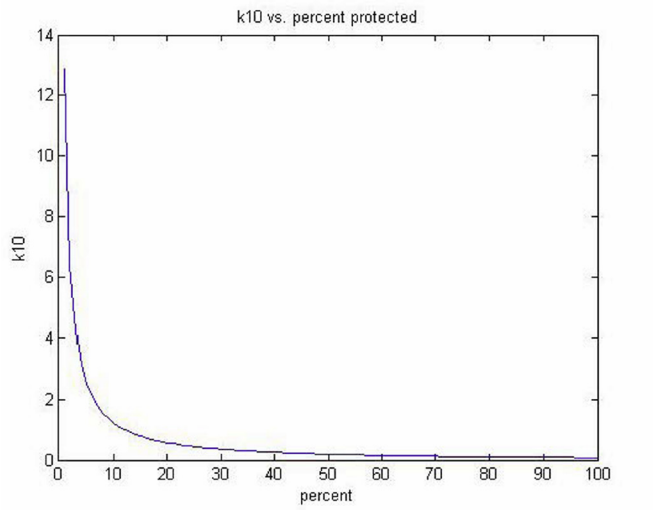

Figure 5. k10 versus oxidation percentage.

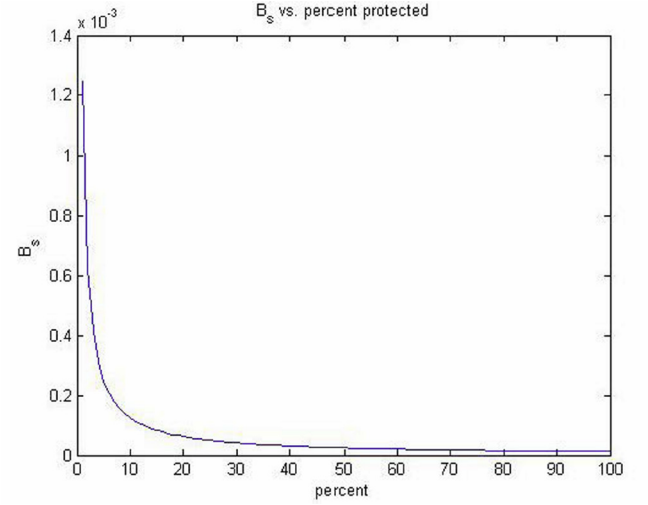

Figure 6. First stabilization value of hydrogen peroxide versus oxidation percentage.

V. CONCLUSION

The major goal of this study was to understand how the given chemical system behaves and to determine whether a mathematical model of the proposed neurocellular protection mechanism was feasible. By modeling the chemical system with a system of differential equations, the actual concentration of each reactant can be graphed versus time and interpreted to confirm physical intuition about the system of reactions. Furthermore, the timescale during which these reactions occur can be deduced. Although there is slight uncertainty in the reaction rates and initial concentrations of the enzymes, a qualitative description of the system is definitely possible. Through the analysis of various graphs, one can determine the dependence of the reactants' second derivative formulae on the reaction rates and also determine the oxidation ratio or percent given very little information about the system. In order to make a model such as the one developed in this paper more quantitative, more information must be known about the cell, including a better approximation of the initial conditions of the reactants' concentrations and a better knowledge of the reaction rates. For example, it would be desirable to know the exact threshold at which enough of the enzyme is nitrated to damage the mitochondria in the cell enough to kill the cell. With this information, treatments of patients who have sustained brain damage could be targeted at preventing the cell from crossing this threshold.

The same analysis could be effectively applied to an even larger subsystem of the cell, stripping off various simplifications and approximations, and furthering our understanding of the chemical processes that occur within stressed cells and in cells in general.

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